Review Article

The role of positron emission tomography in the evaluation and management of musculoskeletal lesions—a narrative review

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Background and Objective: The role of positron emission tomography (PET) in evaluating musculoskeletal lesions has evolved significantly over the past several decades. When combined with conventional imaging, PET can provide substantial value, but understanding its optimal use and potential pitfalls is crucial. This literature review highlights the current role of PET in common bone and soft tissue sarcomas (STS), PET-positive benign lesions, differentiating between benign and malignant lesions, and evaluating skeletal lesions from primary carcinomas. Furthermore, we review the future potential of PET in this evolving landscape.

Methods: In this literature review article, PubMed, Cochrane Library, and Google Scholar databases were searched for studies and reviews on the management of musculoskeletal tumors with PET-computed tomography (CT) scans with focus on bone and STS.

Key Content and Findings: This review elucidates the optimal scenarios for employing PET/CT in managing musculoskeletal tumors and highlights potential pitfalls. A key strength of this study is the correlation of patient case imaging, effectively demonstrating practical applications of PET/CT.

Conclusions: PET imaging serves as a valuable tool for diagnosis, staging, and surveillance of musculoskeletal tumors, particularly sarcomas. With a multidisciplinary approach and ongoing research, PET/CT is poised to become a leading method in the management of musculoskeletal tumors.

Keywords: Orthopaedic oncology; musculoskeletal tumors; soft tissue sarcoma (STS); bone sarcoma; positron emission tomography/computed tomography (PET/CT)

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Introduction

Positron emission tomography (PET) is a noninvasive imaging technique that utilizes the decay properties of certain isotopes (1). Compared with magnetic resonance imaging (MRI) and computed tomography (CT), which assess anatomic and morphologic features, PET can detect the functional and metabolic characteristics of tissue and target specific antigens. First synthesized in 1976 for the mapping of glucose metabolism in the brain, flourine-18 fluorodeoxyglucose (^{18}F-FDG), is the most common positron emitting radiopharmaceutical used in clinical imaging today. ^{18}F-FDG, a radioactive glucose derivative, exhibits increased

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accumulation in most cancer cells due to the increased rate of glycolysis exhibited by cancer cells (1-5). The degree of ^{18}F-FDG uptake by a tumor is expressed by the standard uptake value (SUV), a semiquantitative measure where a higher SUV correlates to an area that is more metabolically active (1,3).

Previously, PET and CT scans were completed separately to depict both metabolic and anatomic features of tumors. However, in 1998, an integrated PET/CT scanner was developed (*Figure 1*). These scanners are now widely used today and studies have shown that PET/CT scans produce more accurate results compared to PET or CT scan alone (4,6-8). The utilization of PET/CT has the potential to enhance tumor detection, staging, response to treatment, and recurrence (8). Over the past two decades, there has been a significant increase in the use of PET/CT in the management of both bone and soft tissue sarcomas (STS). As understanding of various STS and bone sarcomas expands alongside the rising adoption of PET/CT, its applications and indications are expected to broaden. This literature review aims to outline the current applications of PET in common bone and STS, PET-positive benign lesions, differentiation between benign and malignant lesions, and its utility in evaluating skeletal lesions originating from primary carcinomas. This article is in accordance with the Narrative Review reporting checklist (available at https://aoj.amegroups.com/article/view/10.21037/aoj-24-26/rc).

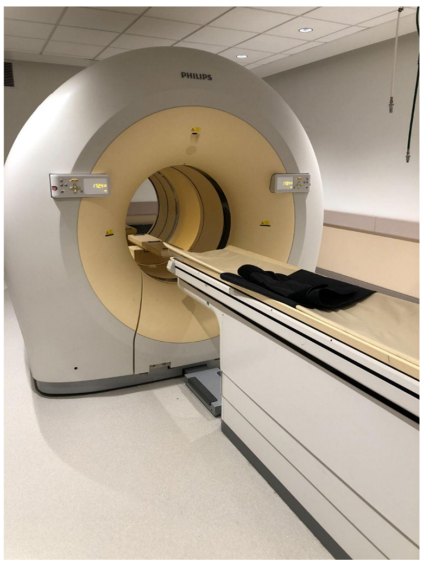

Figure 1 Integrated PET/CT scanner. A PET camera and CT scanner are combined to form one instrument. Patients undergo ^{18}F-FDG PET after receiving ^{18}F-FDG intravenously and then CT is performed without moving the patient using the same table. PET/CT, positron emission tomography/computed tomography; ^{18}F-FDG, flourine-18 fluorodeoxyglucose.

Methods

An extensive review of the literature on PET/CT and musculoskeletal tumors was performed and is summarized in *Table 1*. PubMed, Cochrane Library, and Google Scholar were used to source studies ranging from 1999 to 2024 on May 1, 2024. The keywords used in the search were "PET/CT, Musculoskeletal tumors, soft tissue sarcoma, bone sarcoma, PET/MRI, nuclear imaging". The content from the selected studies and review articles provided the basis for this review. Patient case images were selected from known patient cases to the attending author and were reviewed with a musculoskeletal radiologist.

After exclusions, 18 studies that met the inclusion criteria were analyzed for the review and flowchart can be seen in *Figure 2*. Articles used included retrospective case series, retrospective cohort studies, and meta-analyses. To assess the risk of bias, the Joanna Briggs Institute's tool of Critical

Table 1 Visual representation of how the methods were performed. Annals of Joint template was used to format chart

Items	Specification
Date of search	May 1, 2024
Databases and other sources searched	PubMed, Cochrane Library, and Google Scholar
Search terms	PET/CT, Musculoskeletal tumors, soft tissue sarcoma, bone sarcoma, PET/MRI, nuclear imaging
Timeframe	1999–2024
Inclusion	Retrospective, prospective study, meta-analysis, review article, English article
Selection process	Selected by J.M.P., M.R.D.

PET/CT, positron emission tomography/computed tomography; MRI, magnetic resonance imaging.

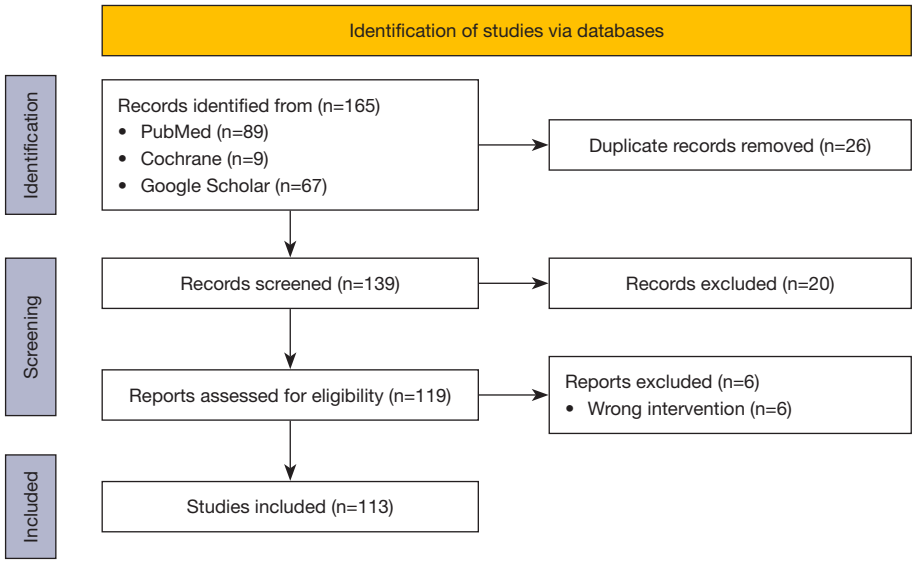

Figure 2 Flowchart for selection of articles for this narrative/literature review. *Annals of Joint* template was used to format chart. After assessment of all returnable studies, with duplicates removed, 113 studies were eligible to be used in this narrative review.

Appraisal Checklist was used and demonstrated the overall risk of bias to be rated as low considering the majority of studies used for this narrative review were meta-analyses.

PET in sarcoma

Diagnosis/grading

While not currently recommended for initial diagnostic workup of soft tissue or bone sarcomas, ^{18}F-FDG PET/CT has demonstrated significant value as an adjunctive tool in interpreting conventional imaging findings of these lesions (9,10). Due to the wide variety of histologic subtypes in STS, and their variable ^{18}F-FDG uptakes, more controversy surrounds the widespread use of ^{18}F-FDG PET/CT for STS compared to bone sarcomas (8). Current guidelines from the National Comprehensive Cancer Network (NCCN) recommend including PET/CT for the workup of symptomatic bone lesions with abnormal radiographs in patients 40 years of age or older (10).

The basis behind using PET/CT in sarcomas is that oncogenic drivers often lead to the upregulation of glucose transporters, resulting in elevated ^{18}F-FDG uptake on PET. The increased metabolic activity of tumors can be semi-quantitively estimated using the maximum standardized uptake value (SUVmax), where higher FDG uptake correlates with higher grade tumors (11). Several studies suggest that ^{18}F-FDG PET/CT can reliably diagnose high-grade bone and STS with overall high sensitivity, specificity and accuracy (12-14). Additionally, statistically significant differences of SUVmax between low-grade and high-grade sarcoma have been reported, however, there is a lack of consensus regarding the optimal SUVmax threshold, with recommendations ranging between 2.4–7.5 (11-16). It is important to note that there are certain high-grade sarcoma subtypes that demonstrate low SUVmax while some low-grade and benign lesions may show high SUVmax values (8).

Some of the earliest studies 25 years ago demonstrated that PET/CT can reliably discriminate between benign and malignant soft tissue and bone lesions, along with low-grade and high-grade malignant lesions of the same histologic subtype. However, PET/CT has proven to be less successful at delineating benign tumors from low-grade malignant tumors (17). This is likely due to the heterogenous nature of sarcoma tumors with diverse histopathologic characteristics that may influence glucose metabolism and ultimately the ^{18}F-FDG uptake. These findings suggest that ^{18}F-FDG PET/CT may not be useful for all sarcoma subtypes.

Overall, while biopsy and histologic exam remains the gold standard diagnostic evaluation, SUVmax has been shown to provide a good estimation of tumor grade with its strong association with the histologic grading, cellularity, p53 expression, and mitotic activity of sarcomas (18). SUVmax can be particularly beneficial in cases in which interobserver variability in pathologic evaluation or when

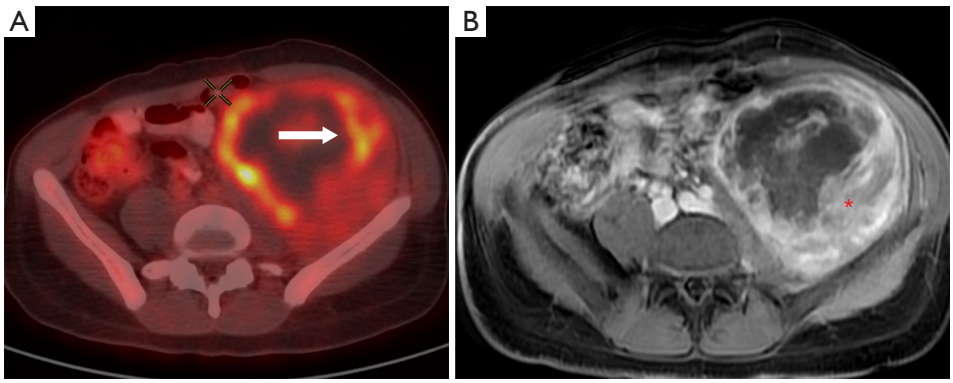

Figure 3 PET/CT and MRI images of a patient with a large heterogenous pelvic soft tissue sarcoma, both showing an area of central necrosis, but a clearly different enhancement/avidity between PET and MRI. (A) Axial PET/CT showing more enhancement (white arrow) of soft tissue lesion than MRI, which will therefore provide a higher yield for histopathological examination. (B) MRI showing less metabolically active tissue along the iliac crest (asterisk) when compared to PET/CT. PET/CT, positron emission tomography/computed tomography; MRI, magnetic resonance imaging.

classification using histopathologic criteria alone is difficult. PET can therefore enhance preoperative prognostic assessment and guide further management (18).

Biopsy

Accurate diagnosis via pathologic confirmation by biopsy is essential for optimal patient care and management. However, the heterogenous nature of STS presents a risk of sampling error when performing a biopsy (19). ^{18}F-FDG PET/CT provides information on the biological activity of tumors, allowing it to guide biopsy to the area of highest uptake, likely pertaining to tumor tissue of the highest-grade (*Figure 3*) (20). Prior studies have demonstrated that most malignant sites, as determined by whole-tumor histology, correlate with biopsy sites identified by ^{18}F-FDG PET/CT (21). Furthermore, representative tissue sampling using ^{18}F-FDG PET/CT minimizes the risk of underestimating tumor grade, which can subsequently affect prognostication as well as management of patients with sarcoma (21).

Staging

Sarcomas are commonly staged using high-resolution chest CT due to their propensity for lung metastasis, with CT demonstrating higher sensitivity compared to ^{18}F-FDG PET/CT (20,22). However, while relatively uncommon, specific sarcoma subtypes have a higher incidence of extrapulmonary metastases to bone and lymph nodes (23). ^{18}F-FDG PET/CT has shown to be superior to conventional imaging modalities in the detection of lymph node and skeletal metastases in the staging of sarcoma patients, allowing for proper disease upstaging and the consequent switch from a local to systemic chemotherapy (24-26). A retrospective study demonstrated that 12% of the patients who underwent FDG PET/CT led to upstaging in the setting of occult lesions on conventional CT and/or MRI studies (27). Furthermore, Mester *et al.* found that use of PET/CT led to a change in management in approximately one-third of patients and was statistically significant in determining prognosis (28). ^{18}F-FDG PET/CT was also useful for disease downstaging due to the lack of ^{18}F-FDG uptake in suspicious appearing lesions on CT scan, particularly lung nodules (29). Thus, ^{18}F-FDG PET/CT can play a pivotal role in detecting metastases at unconventional sites, outside the standard field of view of CT and MRI, excluding disease with equivocal results on conventional imaging (20,30,31).

Prediction of prognosis

Numerous studies have shown baseline tumor SUVmax to be a strong independent predictor of overall survival and clinical outcome (32-36). Sarcoma patients with an SUVmax of ≥10.3 have a 2-fold risk of disease progression and 2.4 times greater risk of morbidity (33). In a study evaluating the prognostic ability of SUVmax in patients with STS of varying histologic malignancy grades, the authors demonstrated an inverse relationship between preoperative tumor SUVmax and the 5-year survival rate (35). Furthermore, a statistically significant correlation has been established

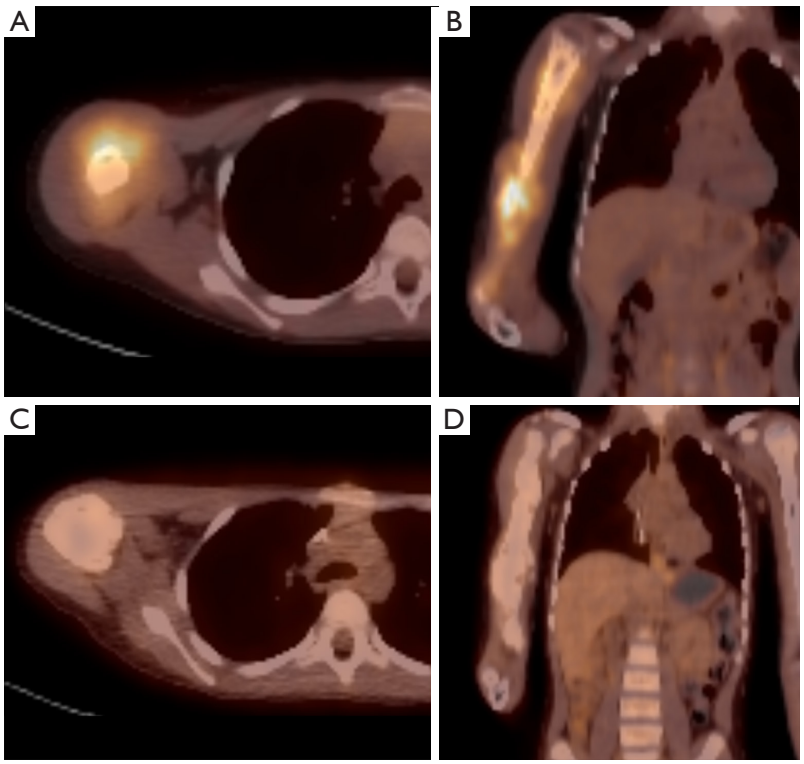

Figure 4 PET/CT images of a patient with osteosarcoma both pre- and post-neoadjuvant treatment. (A) Axial PET/CT before neoadjuvant chemotherapy initiated with SUVmax of 5.7. (B) Coronal PET/CT before neoadjuvant chemotherapy initiated with SUVmax of 5.7. (C) Axial PET/CT after neoadjuvant therapy showing a SUVmax of 3.7, a 65% decrease, which was predictive of a favorable response on histopathological examination in this patient. (D) Coronal PET/CT after neoadjuvant therapy showing a SUVmax of 3.7, a 65% decrease, which was predictive of a favorable response on histopathological examination in this patient. PET/CT, positron emission tomography/computed tomography; SUVmax, maximum standard uptake value.

between SUVmax and histologic grading, cellularity, mitotic activity, P53 expression, mitotic count, and the presence of tumor necrosis; all of which are adverse prognostic factors (15,34). Total lesion glycolysis (TLG) is an additional metabolic parameter derived from ^{18}F-FDG PET/CT that can also be used to predict prognosis in patients with STS. TLG, which combines metabolic and volumetric indices, may be a more accurate predictor of progression-free survival in STS than SUVmax (37). However, there is no current consensus in the advantage of volumetric PET parameters over SUVmax.

Response to treatment

Response to treatment is traditionally defined as a significant decrease in tumor dimensions. However, this definition may not always be accurate in the case of sarcomas as the cytostatic therapies that are often used in sarcoma management, aim to stabilize tumor growth rather than shrink the tumor (38). Therefore, treatment assessment based only on size may be less accurate (32). Tumor tissue can be substituted by necrotic or fibrotic tissue as an effect of therapy leading to either no change or an increase in volume. Thus, a reduction in viable tumor cell fraction does not necessarily equate to a volume reduction (20).

The reduction of metabolic activity measured using the difference between the SUV pre- and post-therapy values has been shown to be a more accurate method for assessing treatment response in sarcoma patients (39). The advantage of ^{18}F-FDG PET/CT lies in its ability to assess therapeutic response early during treatment as the biochemical changes in a tumor usually occur before the morphologic changes. A 35% reduction in SUVmax is capable of predicting a histopathologic response in high-grade sarcomas after one cycle of chemotherapy (*Figure 4*) (40). Additionally, the ability of ^{18}F-FDG PET/CT to identify non-responders early

during treatment can have important clinical implications as it can guide management decisions regarding the need to change treatment regimen and/or reduce the risk of treatment-associated morbidity and patient costs (9).

It should be noted that there have been a few reported cases where significant decreases in ^{18}F-FDG uptake were seen in patients who ultimately did not respond to treatment. The underlying etiology of this phenomenon is unknown and warrants further investigation. Additionally, assessing treatment response in calcified osteosarcoma metastases may pose challenges as these lesions are known to have low or absent ^{18}F-FDG uptake at baseline (10,41,42). Furthermore, the size of a calcified metastasis is not expected to reduce, and even if complete tumor response has occurred, the lack of change in size also hinders differentiation of viable from non-viable tumor (10).

As the understanding of the genetic and molecular nuances of various sarcoma histotypes continues to grow, FDG PET/CT, along with other radiotracers, will become invaluable to the treatment and monitoring of sarcomas.

Recurrence

As with any other malignancy, sarcomas can recur both locally and systemically. The majority of recurrences in sarcoma patients develop within two years following primary tumor resection, underscoring the importance of surveillance imaging in patient management (20). Early detection of local or distant recurrences allows prompt initiation of further treatment. When utilizing anatomic imaging alone, it can be difficult to detect recurrence with effective sensitivity and specificity as posttreatment changes and metal artifacts may obscure disease recurrence and complicate the interpretation of conventional imaging. For this reason, ^{18}F-FDG PET/CT can be a valuable adjunct to anatomic imaging for disease monitoring. A recent meta-analysis including thirty-one studies revealed that FDG PET/CT had a high specificity (92.6%) and sensitivity (89.9%) for detecting local recurrence after treatment in patients with Ewing sarcoma (ES) (43,44). Additionally, while not statistically significant, Park *et al.* demonstrated that PET/CT exhibited a higher sensitivity and specificity when compared to MRI for detecting local recurrence (45). While these results were not statistically significant, it was recommended PET/CT and MRI may be used in conjunction, particularly in difficult cases where metallic prosthesis may obscure findings on CT and MRI (27,43). It is important to note a potential downfall of PET/CT in detecting recurrence in patients that are post-surgical or post-radiation, as changes may persist for several months to years after treatment and need to be considered when evaluating the operative/treated area.

Common bone sarcomas

Osteosarcoma

^{18}F-FDG PET/CT can serve as a potential powerful tool in the staging of osteosarcoma both at diagnosis and during surveillance. A recent meta-analysis evaluating the effectiveness of ^{18}F-FDG PET/CT in the detection and staging of osteosarcoma demonstrated excellent pooled sensitivity and specificity for detecting bone and distant metastases (46). Compared with bone scintigraphy (BS), ^{18}F-FDG PET/CT had an increased sensitivity, specificity, and diagnostic accuracy to identify bone metastases in patients with osteosarcoma (*Figure 5*) (47-59). ^{18}F-FDG PET/CT is particularly more sensitive than BS for the detection of lesions at an open physis due to the high physiologic radiotracer uptake in BS which can obscure metastases on routine BS (47). As previously mentioned, with respect to pulmonary metastases, the sensitivity of ^{18}F-FDG PET/CT is lower than conventional chest CT, particularly for small nodules (*Figure 6*) (50).

^{18}F-FDG PET/CT also provides value in the surveillance for recurrent osteosarcoma due to its ability to effectively distinguish between local recurrence and postsurgical change. Lesions exhibiting both an elevated SUVmax and an increase in SUVmax greater than 75% after therapy completion, have been shown to be diagnostic for local recurrence (51). In addition, ^{18}F-FDG PET/CT has been shown to detect recurrence when MRI and BS were unable to do so (52).

^{18}F-FDG PET/CT can also be utilized as a noninvasive method to assess the response to neoadjuvant chemotherapy. A meta-analysis demonstrated that a post-treatment SUVmax of $\leq$2.5, and the ratio of SUVmax at diagnosis and that following neoadjuvant chemotherapy of $\leq$0.5, were both strong predictors of histologic response at the time of limb-sparing surgery in patients with osteosarcoma (53). Additionally, using the percent change in SUVmax before and after one cycle of presurgical chemotherapy can predict the clinical outcome of extremity osteosarcoma (*Figure 7*) (54).

ES

There is growing data supporting the utility of ^{18}F-FDG PET/CT in the staging and surveillance of patients with ES

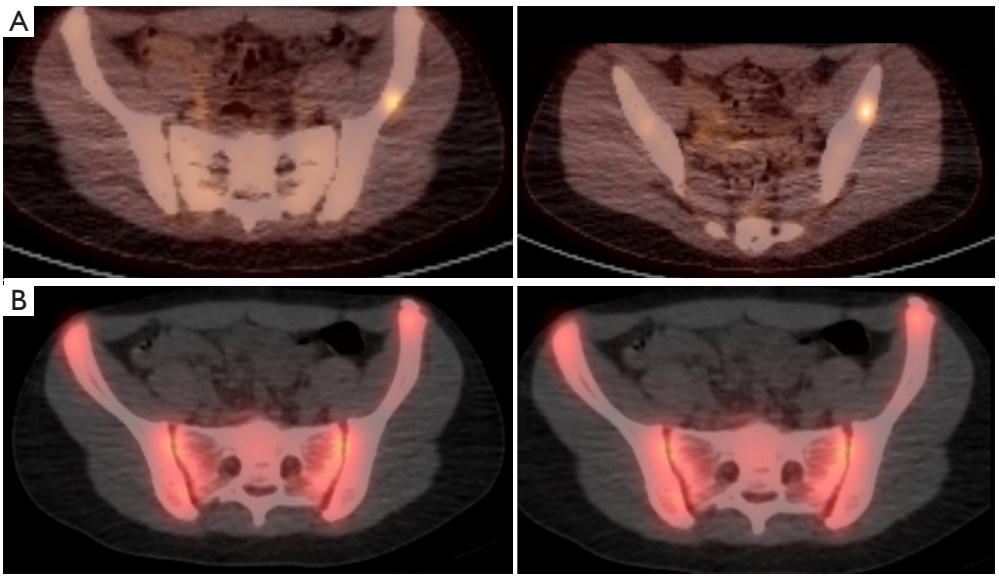

Figure 5 Radiographic images showing the difference in diagnostic accuracy for metastatic detection between PET/CT and BS. (A) Axial slices of PET/CT imaging demonstrate a left ilium metastasis in a patient with Osteosarcoma. (B) Axial images from BS which fail to demonstrate this metastasis. PET/CT, positron emission tomography/computed tomography; BS, bone scintigraphy.

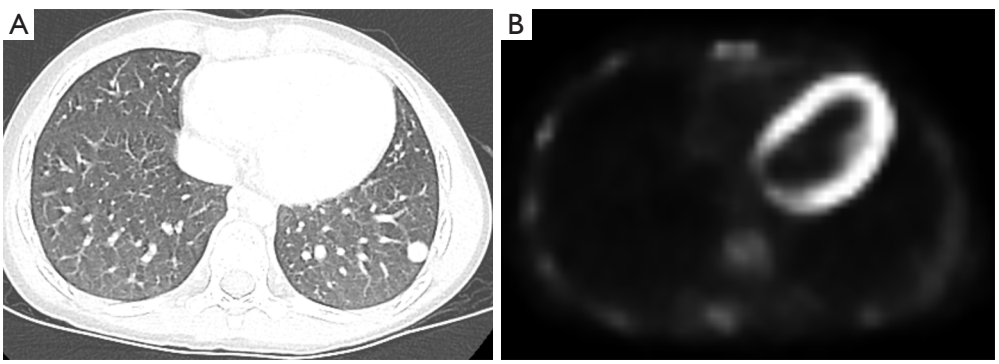

Figure 6 CT chest and PET/CT scan of a patient with osteosarcoma, both studies were taken on the same date. (A) Axial CT chest demonstrating an obvious pulmonary nodule. (B) Axial PET/CT demonstrating difficulty to visualize a nodule on the same patient. CT, computed tomography; PET, positron emission tomography.

(*Figure 8*). ^{18}F-FDG PET/CT has shown to be superior to BS in detecting bone metastases in all areas except the skull, with a higher sensitivity (96% *vs.* 78%), specificity (84% *vs.* 90%), and accuracy (87% *vs.* 82%) (55). Similarly, a recent meta-analysis evaluating patients with ES demonstrated a pooled sensitivity of 91% and a specificity of 98% for ^{18}F-FDG PET/CT in the detection of skeletal metastases (56).

Currently, patients with newly diagnosed ES undergo an invasive procedure with a blind bone marrow biopsy (BMB) of the posterior iliac crest. A recent study comparing BMB and PET/CT showed that the sensitivity, specificity, positive and negative predictive values of ^{18}F-FDG PET/CT were all higher than that of BMB (90.6%, 100%, 100%, 95.4% *vs.* 53.1%, 87.1%, 94.4% and 80.6% respectively) (57). These findings indicate that ^{18}F-FDG PET/CT may be a valuable substitute for ES patients.

In the surveillance of patients with ES, ^{18}F-FDG PET/CT has proven valuable for detecting local and distant disease recurrence (58,60). Patients with a high pre-treatment SUVmax (≥6) generally experience poor response to

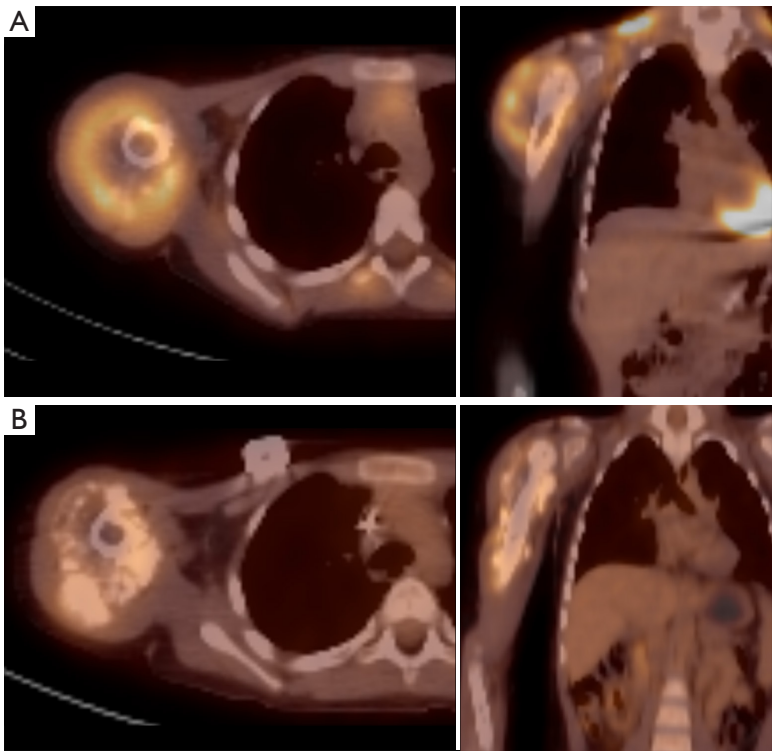

Figure 7 PET/CT images of a 6-year-old patient with proximal humerus osteosarcoma, both pre- and post-neoadjuvant chemotherapy. This patient ultimately required shoulder disarticulation. (A) Axial and coronal PET/CT scans demonstrating proximal humerus osteosarcoma with SUVmax of 5.7. (B) Axial and coronal PET/CT scans, after neoadjuvant therapy demonstrating no significant response. In fact, there is an increase of SUVmax to 6.4. PET/CT, positron emission tomography/computed tomography; SUVmax, maximum standard uptake value.

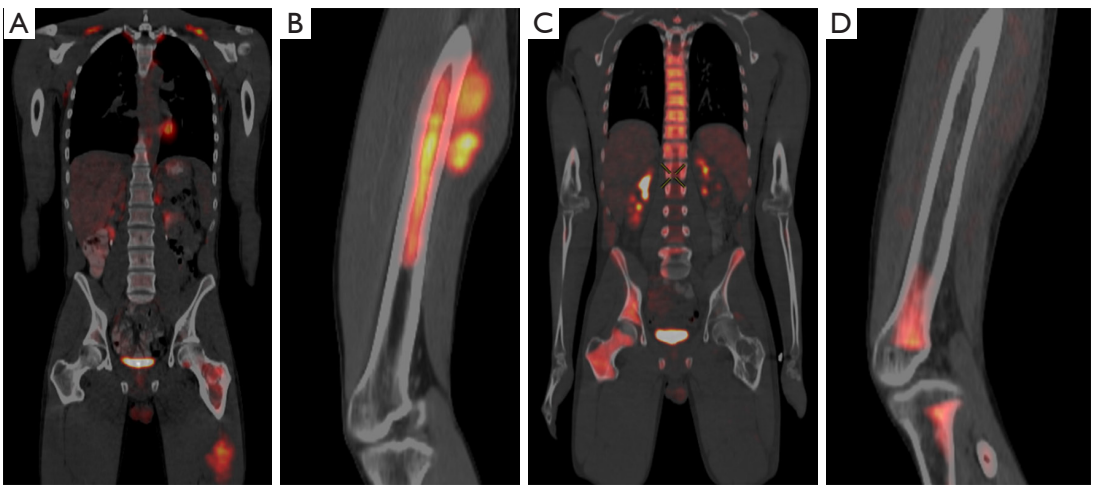

Figure 8 ^{18}F-FDG integrated PET/CT images of a biopsy proven Ewing sarcoma in a 21-year-old male obtained pre- and post-neoadjuvant chemotherapy. (A) Coronal PET/CT image obtained prior to neoadjuvant therapy demonstrating extensive ^{18}F-FDG uptake throughout his left proximal femur, correlating with tumor. (B) Sagittal PET/CT image obtained prior to neoadjuvant therapy demonstrating extensive ^{18}F-FDG uptake throughout his left proximal femur, correlating with tumor. (C) Coronal PET/CT image obtained after neoadjuvant therapy demonstrating near complete resolution in his left proximal femur. (D) Sagittal PET/CT image obtained after neoadjuvant therapy demonstrating near complete resolution in his left proximal femur. ^{18}F-FDG, flourine-18 fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography.

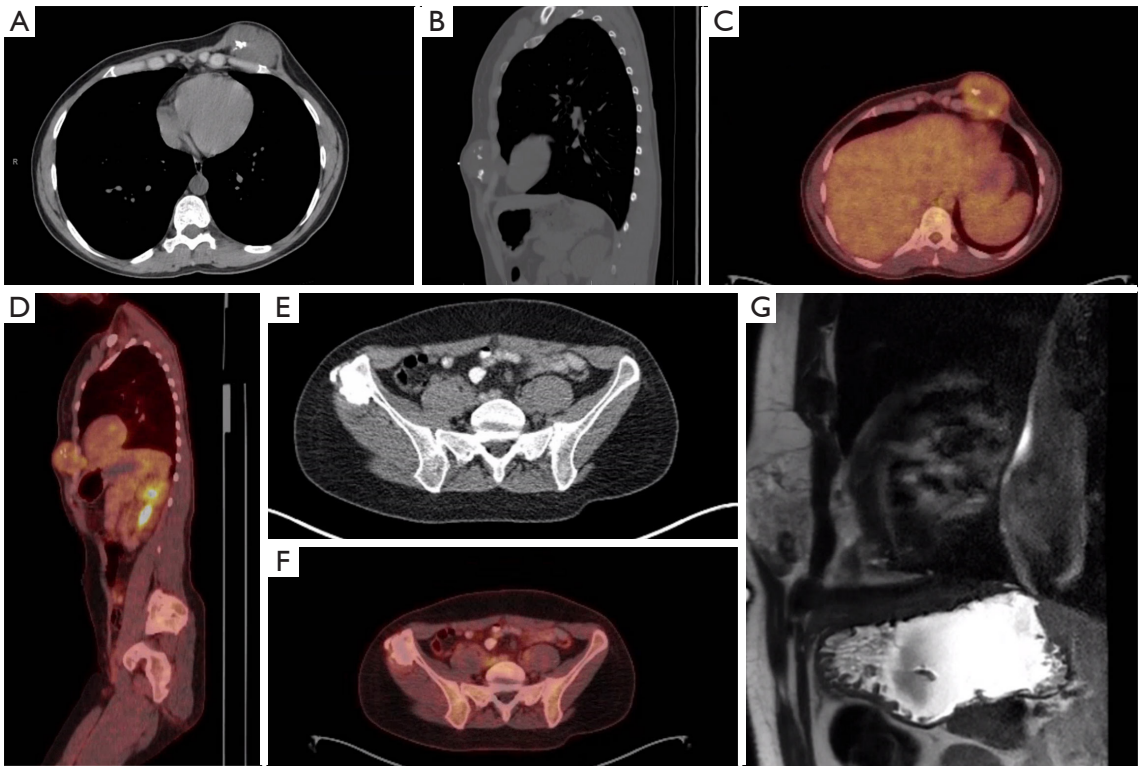

Figure 9 Thirty-year-old female with past medical history of MHE who presented with an anterior chest wall mass. Axial (A) and sagittal (B) CT pre-treatment images are shown with their corresponding axial (C) and sagittal (D) PET/CT imaging. Sagittal (G) MRI also shown. The PET/CT with SUVmax of 3.2 is suggestive of an underlying malignancy, such as malignant transformation in a patient with known MHE. The axial (E) CT and its corresponding axial (F) PET/CT of this same patient demonstrates a right ilium lesion with an SUVmax of 1.2, which is indicative of a non-malignant lesion, likely osteochondroma secondary to her known MHE. MHE, multiple hereditary exostosis; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography; SUVmax, maximum standard uptake value.

treatment and have a decreased overall survival. Conversely, those with low pre-treatment SUVmax tend to have a better response to neoadjuvant chemotherapy, leading to an improved overall and progression-free survival (59,60). Furthermore, patients with a metabolic reduction ≥55% have a significantly higher rate of 3-year event-free survival (61).

Chondrosarcoma

Due to their wide range of variability, chondroid lesions can be difficult to characterize both radiologically and histologically, and distinguishing malignant cartilage lesions from benign ones on conventional imaging further complicates the diagnosis of chondrosarcoma. Results from several studies suggest that ^{18}F-FDG PET/CT is valuable in identifying malignant lesions where an SUVmax <2 can be used to exclude chondrosarcoma with high accuracy while an SUVmax >4.4 is strongly suggestive of malignancy (*Figure 9*) (62-64).

^{18}F-FDG PET/CT can accurately discriminate low-grade chondrosarcomas (LGCS) from intermediate/high-grade chondrosarcomas by using an SUVmax cutoff of 3.7 and between intermediate/high-grade chondrosarcoma from dedifferentiated chondrosarcoma using an SUVmax cutoff of 7.7 (*Figure 10*). However, there exists a significant range in SUVmax values between 2.0 to 4.4 where ^{18}F-FDG PET/CT has a poor specificity in differentiating between benign cartilage lesions and LGCS (62-66).

Common STS

Rhabdomyosarcoma

Primary tumoral metabolic activity and the presence

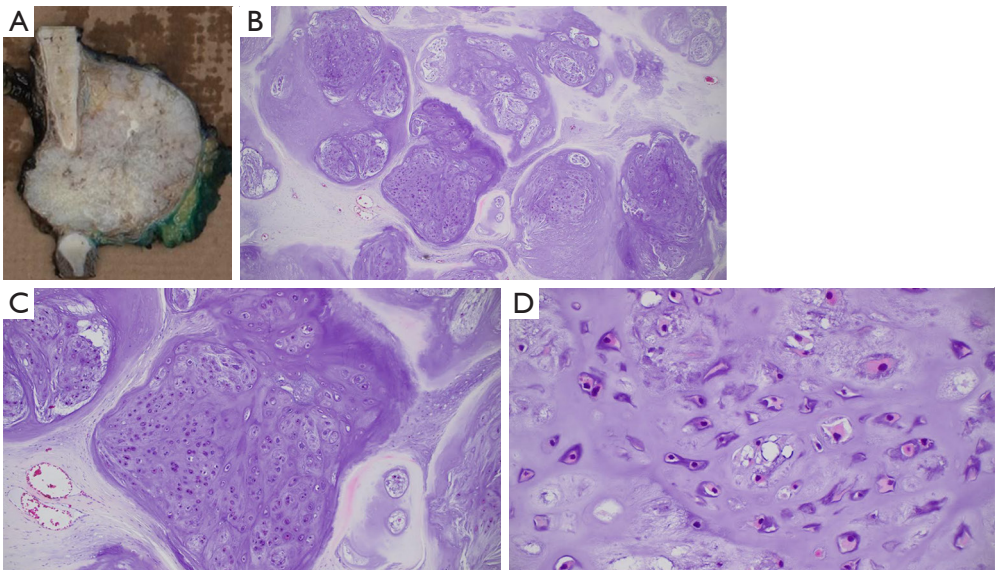

Figure 10 Images correlating to a 30-year-old patient with chondrosarcoma with SUVmax of 3.2. These images demonstrate that PET/CT can accurately differentiate low-grade chondrosarcomas from intermediate/high-grade chondrosarcomas using a 3.7 SUVmax cutoff. (A) Gross specimen of chondrosarcoma. (B) Histologic analysis demonstrates a low-grade chondrosarcoma which is consistent with this patient's SUVmax of 3.2 (HE, 4×). (C) Histologic analysis demonstrates a low-grade chondrosarcoma which is consistent with this patient's SUVmax of 3.2 (HE, 20×). (D) Histologic analysis demonstrates a low-grade chondrosarcoma which is consistent with this patient's SUVmax of 3.2 (HE, 40×). SUVmax, maximum standard uptake value; PET/CT, positron emission tomography/computed tomography; HE, hematoxylin and eosin.

of nodal and/or extra-nodal metastases are the major determinants of patient survival in rhabdomyosarcoma (67). Therefore, accurate initial staging is imperative for proper prognostication. Due to its proven ability to identify areas of metastatic disease, particularly in the lymphatic system, ^{18}F-FDG PET/CT has evolved into a valuable tool for the evaluation of patients with rhabdomyosarcoma. During initial staging,^{18}F-FDG PET/CT has been shown to have improved sensitivity and specificity when compared to conventional imaging in the detection of nodal and skeletal metastases (*Figures 11,12*) (67,68). However, ^{18}F-FDG PET/CT should not replace histopathologic examination of lymph node tissue when evaluating nodal disease in these patients. A recent study compared the utility of sentinel lymph node biopsy with ^{18}F-FDG PET/CT for the identification of nodal metastases in patients with pediatric and adolescent STS. Histological findings of the excised lymph nodes were correlated with preoperative ^{18}F-FDG PET/CT imaging. Lymph node biopsy identified tumors in 7 of the 28 patients. Of these patients, three had normal ^{18}F-FDG PET/CT findings (69). Thus, while PET/CT is very helpful in diagnosis, it still should be used in conjunction with biopsy.

Liposarcoma

Lipomatous tumors range from benign to malignant lesions, requiring precise differentiation for appropriate management. MRI is valuable for distinguishing benign lipomas from liposarcomas, though differentiating benign from well-differentiated malignant lesions remains diagnostically challenging. ^{18}F-FDG PET/CT can serve as an adjunct to conventional imaging through its ability to evaluate both metabolic and structural characteristics. Liposarcoma tumor grade correlates with the degree of metabolic activity, with higher grade tumors having greater ^{18}F-FDG uptake. However, there is overlapping metabolic activity of benign and malignant lipomatous tumors (70).

It is important to note that due to the low glycolytic activity of ^{18}F-FDG in myxoid liposarcoma, PET/CT may lack sufficient sensitivity in diagnosing and detecting osseous metastasis (71). Therefore, patients affected by myxoid liposarcoma should be screened with CT of the chest, abdomen and pelvis and MRI of the spine or whole-

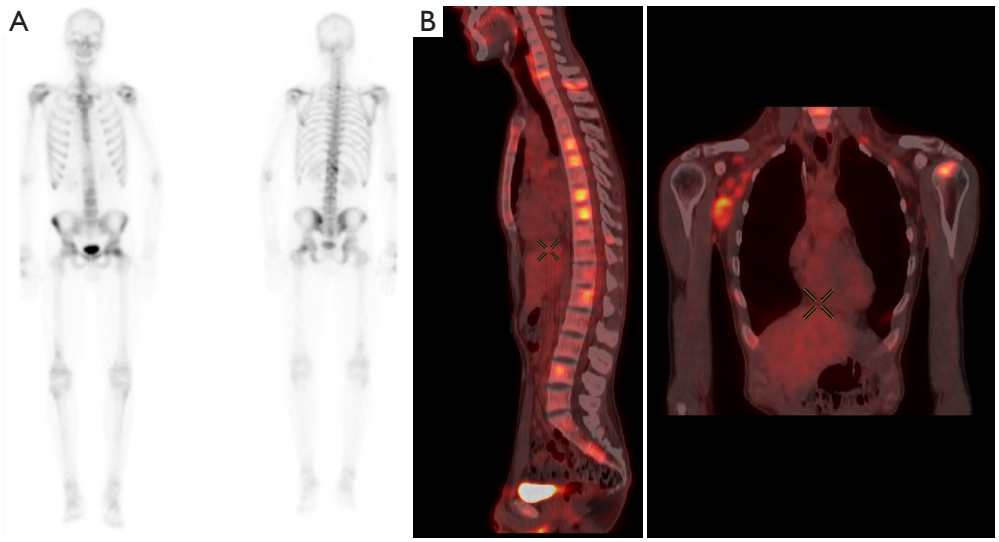

Figure 11 Comparison of BS and PET/CT in a patient with biopsy proven metastatic rhabdomyosarcoma. (A) Bone scintigraphy is not able to detect multiple metastatic lesions to the spine. (B) PET/CT images not only reveal the lesions in the spine but also reveal metastatic disease to the axillary lymph nodes. BS, bone scintigraphy; PET/CT, positron emission tomography/computed tomography.

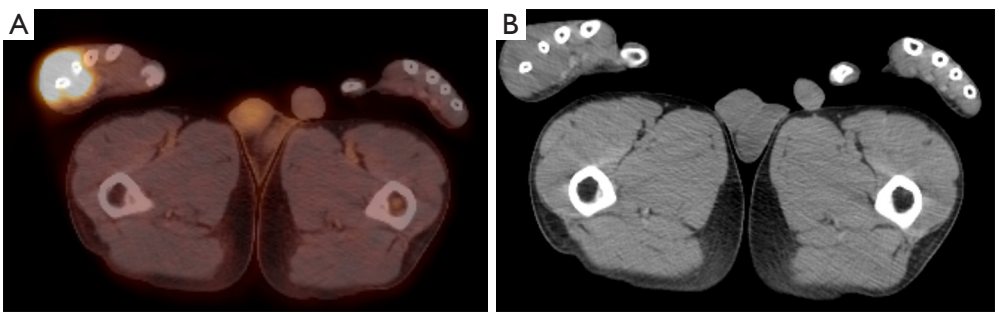

Figure 12 PET/CT and CT scan of a patient with alveolar rhabdomyosarcoma with extra-nodal, skeletal metastases to the right hand. (A) Axial PET/CT shows that the lesions are more conspicuous on the PET/CT when compared to concurrent CT. (B) CT of right hand showing less conspicuous lesions as seen on PET/CT. PET/CT, positron emission tomography/computed tomography.

body BS to assess for distant bone metastases (10,72).

Malignant peripheral nerve sheath tumors (MPNST)

Identifying malignant transformation of peripheral nerve sheath tumors can be difficult even when utilizing CT, MRI, and clinical evaluation. Furthermore, excisional biopsy is not without danger to adjacent or adherent neurovascular structures. One of the best studied areas of FDG PET/CT use is its ability to differentiate benign from MPNSTs (43). This is of particular interest to patients with neurofibromatosis who are at high risk for sarcomatous transformation. A cutoff of 2.5 g/mL for neurofibromatosis type 1 (NF1) patients was shown to differentiate benign from malignant lesions (73,74). Along with SUV, TLG and total metabolic tumor volume have been shown to clinically identify sarcomatous transformation in patient with NF1 (73,74). The role of FDG PET/CT is promising for MPNST, but its ability to differentiate schwannomas from MPNSTs and other malignant sarcomas is lacking. Schwannomas can present with a wide range of FDG uptake values, which forces schwannoma to be on the differential of any suspicious appearing nerve sheath tumor with any SUV FDG uptake value (75). Interestingly, new retrospective studies have shown fluorine-18 alpha-methyl tyrosine (FMT) PET imaging to be the more

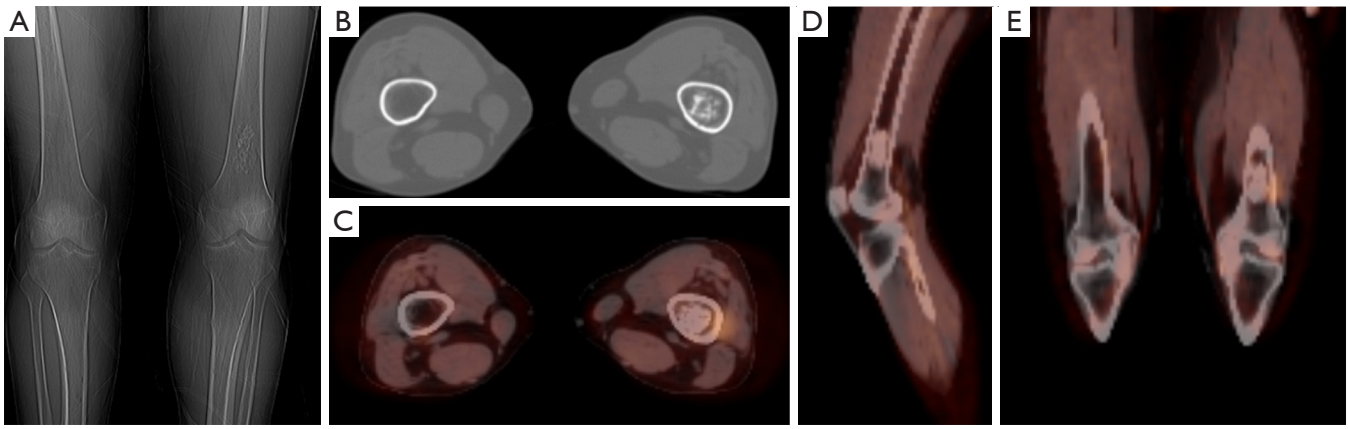

Figure 13 Images demonstrate a patient with a benign enchondroma which has low uptake on PET/CT with SUVmax <1.0. (A) Plain radiograph of patient's benign enchondroma. (B) Corresponding axial CT of benign enchondroma. (C) Axial PET/CT of benign enchondroma. (D) Sagittal PET/CT of benign enchondroma. (E) Coronal PET/CT of benign enchondroma. SUVmax, maximum standard uptake value; PET/CT, positron emission tomography/computed tomography.

reliable technique in differentiating benign schwannoma from malignancy (76). The role of FDG-PET and FMT-PET imaging is promising and should be utilized when screening and staging patients with neurofibromatosis type I or aggressive-appearing peripheral nerve sheath tumors in order to detect early malignant transformation.

PET in benign lesions and pitfalls

Differentiating benign from malignant lesions

As discussed previously, ^{18}F-FDG PET/CT can reliably distinguish between benign and malignant musculoskeletal lesions (*Figure 13*) (77). Optimal cutoff ranges have been suggested anywhere from 2.4 to 7.5 SUVmax (14-16). Furthermore, there also is a significant overlap in values between low-grade malignant lesions and certain benign lesions. Therefore, ^{18}F-FDG PET/CT should be interpreted within the broader clinical context for each individual patient, frequently in conjunction with other imaging modalities (15,17).

Lodge *et al.* demonstrated that ^{18}F-FDG kinetics can also be used to differentiate benign tumors from malignant variants. They found that STSs achieve the maximal ^{18}F-FDG uptake 4 hours following the radiotracer injection, whereas benign lesions reached peak uptake after only 30 minutes. This method showed a sensitivity and specificity of 100% and 76%, respectively (78).

There are several known benign musculoskeletal lesions that are metabolically active and demonstrate high ^{18}F-FDG uptake (*Table 2*) (22,43,79). A common finding within many of the processes seen in *Table 2* is the increased presence of histiocytic and giant cells which may be responsible for the high ^{18}F-FDG uptake (80). Therefore, the metabolic activity (SUVmax) on PET/CT should not be the sole deciding factor when distinguishing between a benign versus malignant tumor.

Various infectious and inflammatory processes may lead to increased focal uptake of ^{18}F-FDG potentially leading to misinterpretation as malignancy (*Table 2*) (22,79,81,82). At the site of inflammation or infection, inflammatory cells such as neutrophils, macrophages, and lymphocytes, demonstrate elevated ^{18}F-FDG uptake by way of increased expression of the glucose membrane transporter (81). Chronic disease processes like osteomyelitis and granulomatous diseases may further prompt intense reactive nodal avidity, which may mimic malignancy. Longstanding indwelling catheters and lines can also show increased ^{18}F-FDG uptake as they can generate a foreign body-like inflammatory response, characterized by the formation of granulation tissue with intense ^{18}F-FDG uptake (81). Similarly, granulomas in the subcutaneous soft tissues and muscles are commonly seen in patients receiving injections, which can also demonstrate a foci of ^{18}F-FDG accumulation (82).

Post-surgical changes are another source of increased ^{18}F-FDG uptake. Initially after surgery, there is formation of granulation tissue in and around the surgical bed which mainly consists of inflammatory cells, small vessels, and fibroblasts—all of which can increase ^{18}F-FDG uptake on PET/CT (83).

Table 2 A list of benign bone and soft tissue lesions and inflammatory conditions which demonstrate avid ^{18}F-FDG uptake that can be falsely interpreted as malignancy

Benign processes with increased ^{18}F-FDG uptake
Bone lesions
Giant cell tumor of bone
Langerhans cell histiocytosis
Fibrous dysplasia
Non-ossifying fibromas
Chondroblastoma
Osteoid osteoma
Chondromyxoid fibroma
Brown tumor
Desmoplastic fibroma
Hemangioma
Intra-osseous lipoma
Eosinophilic granuloma
Aneurysmal bone cyst
Soft tissue lesions
Giant cell tumor of tendon sheath
Pigmented villonodular synovitis
Desmoid tumor
Inflammatory cells
Soft tissue abscesses
Osteomyelitis
Discitis
Septic arthritis
Prosthetic joint infections
Pneumonia
Sinusitis
Tuberculosis
Infectious mononucleosis (Epstein Bar virus)
Fungal or granulomatous diseases
Shingles
Myositis
Decubitus ulcer
Surgical wound (within 3 months of procedure)

^{18}F-FDG, flourine-18 fluorodeoxyglucose.

Similarly, post-radiation changes, marrow rebound after chemotherapy, or use of granulocyte colony-stimulating factors, demonstrate elevated ^{18}F-FDG uptake (82). ^{18}F-FDG avidity typically remains elevated for an average of 3 months post-treatment, after which uptake gradually decreases as the inflammation subsides (22). It is imperative to understand the time-dependent decrease in uptake when interpreting post-treatment imaging, especially if performed within 3 months of an intervention.

A complete clinical history, physical examination, correlation with anatomic imaging, and knowledge of potential causes of misinterpretation on PET/CT can increase diagnostic accuracy and improve the quality of patient care.

PET in metastatic bone disease

Detection of skeletal metastases from primary carcinomas

Skeletal metastases originating from primary carcinomas are the most common malignant lesion involving osseous structures and are a leading cause of morbidity and adversely impact a patients' quality of life. Metastatic bone lesions weaken the structural integrity of the bone, leading to an increase in the risk for skeletal-related events (SREs) such as pathologic fracture, spinal cord compression, hypercalcemia of malignancy, and severe bone pain requiring palliative radiotherapy or surgery (84). Early detection of skeletal metastases is therefore pivotal for the optimal management of patients with carcinomas.

BS has been the most commonly used technique for the detection of skeletal metastases due to its ability to provide visualization of the entire skeleton within a reasonable amount of time and cost (25). BS has the ability to diagnose bone metastases with high sensitivity, but its specificity is limited, likely because tracer accumulation in BS reflects the metabolic reaction of bone to several disease processes including neoplasms, trauma, and inflammation (85). Additionally, BS can provide false-negative findings when purely osteolytic metastases are growing rapidly, when bone turnover is slow, or when the site has decreased blood flow (86). Studies comparing BS and other conventional imaging with ^{18}F-FDG PET/CT have shown a distinct advantage of ^{18}F-FDG PET/CT in terms of sensitivity and specificity for the detection of bone metastases from carcinomas (25,86,87).

While ^{18}F-FDG PET/CT is more sensitive for the detection of osteolytic metastases, its sensitivity for detecting osteoblastic metastases is reduced compared to BS, likely secondary to different metabolic characteristics of osteolytic

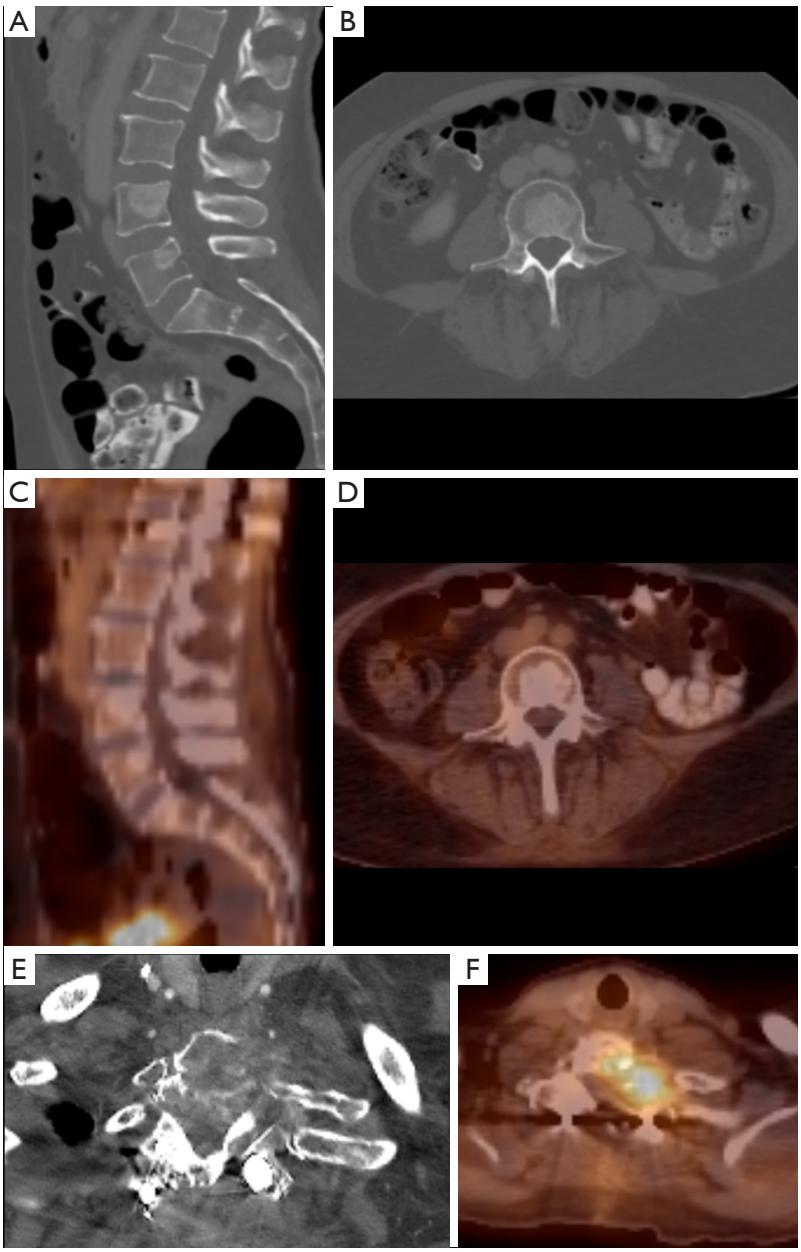

Figure 14 Sixty-nine-year-old female with metastatic breast cancer with mixed osteolytic and osteoblastic spinal metastases. Sagittal (A) and axial (B) CT scans demonstrating blastic lesions in L3/L4 vertebral bodies. The corresponding sagittal (C) and axial (D) PET/CT scans show minimal uptake within the blastic lesions with SUVmax of 2.0. In comparison, the lytic lesion seen in the vertebral body of T11 on the axial (E) CT and axial (F) PET/CT demonstrates significant fluorodeoxyglucose uptake, with an SUVmax of 6. SUVmax, maximum standard uptake value; PET/CT, positron emission tomography/computed tomography.

versus osteoblastic metastases (88). Osteoblast activity and proliferation in sclerotic metastases results in increased bone matrix and a relative decrease in cell density. Therefore, such lesions may have decreased metabolic activity leading to lower FDG accumulation (85,89). This may limit the use of ^{18}F-FDG PET/CT for the evaluation of osteoblastic lesions from prostate, breast, or other primary tumors that tend to develop bone-forming metastases (*Figure 14*).

The development of novel radiopharmaceuticals has enabled clinicians to overcome the aforementioned limitations.

For the imaging of bone metastases, the use of additional radiotracers, such as fluorine-18 sodium fluoride (^{18}F-NaF) has been increasing in clinical practice as it shows high and rapid bone uptake (85). ^{18}F-NaF is an analog for the hydroxyl ion in the bone matrix. The fluoride ion exchanges with a hydroxyl ion on the surface of the hydroxyapatite matrix of bone to form fluorapatite. Fluorapatite then migrates into the crystalline matrix of bone where it is retained until the bone is remodeled (90). Thus, utilization of additional radiotracer ^{18}F-NaF reflects areas of enhanced bone remodeling seen in bone forming tumors (91). When comparing the efficacy of ^{18}F-NaF PET/CT, ^{18}F-FDG PET/CT, and BS in the detection of bone metastases in patients with lung, breast and prostate carcinoma, ^{18}F-NaF PET/CT was shown to have the highest sensitivity and negative predictive value in all 3 malignancies (92). Similarly, a lesion-based analysis showed that ^{18}F-NaF PET/CT is the most sensitive (100%) and specific (98%) method in the detection of bone metastases in patients with lung cancer (93). Furthermore, the co-administration of both ^{18}F-NaF and ^{18}F-FDG provides a promising approach as ^{18}F-NaF PET/CT provides superior image quality for evaluation of skeletal disease extent, whereas ^{18}F-FDG PET/CT allows enhanced detection of extra-skeletal disease (94). However, further research and evaluation are necessary before routine clinical adoption.

The development of Gallium-68 labeled prostate specific membrane antigen (^{68}Ga-PSMA) PET ligand has been significant for patients with prostate cancer (66). Ga-PSMA PET/CT has proven to be an excellent imaging technique for staging of patients with primary prostate cancer, demonstrating superiority over BS in the detecting skeletal metastases (95,96). Irrespective of the radiopharmaceutical agent used, cross-sectional imaging and hybrid imaging with CT enhances both the sensitivity and specificity of bone imaging in the context of metastatic bone disease.

Pathological fracture risk assessment

Assessing pathological fracture risk is critical to reduce complications and optimize the care of patients with metastatic bone disease. Prophylactic fixation of proximal femoral lesions has been proven to improve quality of life and patient survival rate in addition to decreasing overall healthcare costs (97). However, the prediction of an impending pathologic fracture remains a significant clinical challenge. Mirels' score is a commonly used tool which uses both radiographic and clinical risk factors to predict pathologic fracture risk (98). While its sensitivity is superior to clinical judgement, its specificity is suboptimal. The development and use of newer quantitative computed tomography (QCT) based techniques that combine three-dimensional CT imaging and structural analysis such as finite element (FE) and computed tomography rigidity analysis (CTRA), have been successful and proven to be superior to Mirels' score, but widespread use is unlikely in the near future due to expense and accessibility barriers (98,99).

^{18}F-FDG PET/CT has been recently evaluated as a tool to assess femoral pathologic fracture risk in patients with metastatic breast cancer (*Figure 15*) (97). Quantitative measures of FDG avidity were used to identify subsequent fracture risk. The volumetric measurement, TLG, which accounts for both size and intensity of FDG avidity, yielded sensitivity and specificity values of 85% and 80% respectively. Furthermore, a TLG cutoff of 81 could differentiate between patients with a risk of impending pathologic fracture from those at low risk with an accuracy of 83% (97,99). Such application of quantitative FDG PET imaging is promising. However, additional studies are needed to validate these results.

Current guidelines on appropriate use of PET imaging for musculoskeletal tumors

The NCCN guidelines recommend BS and/or PET/CT scan for whole-body staging, restaging after chemotherapy, and for surveillance of osteosarcoma and ES. Furthermore, they suggest that under certain circumstances, PET may be useful in the staging, prognostication, grading, and determining response to therapy in extremity/trunk STS (100,101). The Royal College of Radiologists and the Royal College of Physicians similarly put forth evidence-based indications for the use of PET/CT in the United Kingdom. They support the use of PET/CT in treatment response assessment and the staging of high-grade sarcomas, such as ES, rhabdomyosarcoma, and synovial sarcoma (101). Furthermore, in their appropriateness criteria for follow-up of malignant or aggressive musculoskeletal tumors, the American College of Radiology suggested that ^{18}F-FDG PET/CT can be a useful problem-solving tool if another study is equivocal (102).

Future directions with combining PET and MRI

New integrated PET/MRI systems potentially offer great

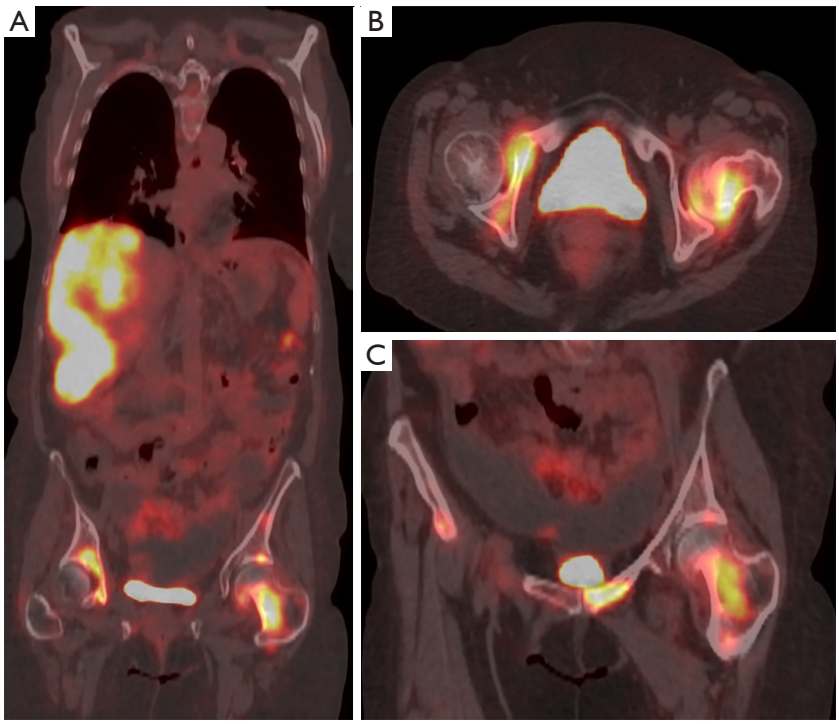

Figure 15 Biopsy proven metastatic breast cancer in a 64-year-old female. Integrated PET/CT images reveal increased ^{18}F-FDG uptake, SUVmax of 11.2, in the left femoral neck correlating with a metastatic lesion. The patient sustained a pathological femoral neck fracture 6 days after these images were obtained. (A) Coronal PET/CT demonstrating increased uptake in right proximal femur. (B) Axial PET/CT with increased uptake in femoral neck. (C) Coronal PET/CT demonstrating increased uptake in right proximal femur. PET/CT, positron emission tomography/computed tomography; ^{18}F-FDG, flourine-18 fluorodeoxyglucose; SUVmax, maximum standard uptake value.

promise and possible advantages over PET/CT. Hybrid PET and MRI systems aim to combine the high-resolution soft-tissue information from MRI with functional and molecular information from PET (103). PET/MRI, which avoids ionizing radiation, may offer a preferable alternative to PET/CT, particularly for pediatric patients and individuals with conditions such as Li-Fraumeni syndrome that predispose them to cancer from ionizing radiation exposure (104). Furthermore, the superior soft tissue contrast resolution and multiparametric techniques of MRI, in comparison with CT, provides additional benefit (50). PET/MRI has the potential to decrease the overall amount of diagnostic studies sarcoma patients undergo and thereby increase the efficiency of workup. The ability of MRI to visualize soft tissue enables early detection of an infiltrative bone marrow process, prior to extension to cortical bone and infiltration of adjacent structures (85).

Despite promising research, PET/MRI holds its own challenges and limitations. Widespread application is currently restricted in part due to the limited availability of the systems and challenges in workflow and reimbursement (103). Additional limiting factors of MRI include poor assessment of the lungs and cortex of bone susceptibility to motion or other artifacts, longer scan times, and more contraindications in comparison to CT (50). PET/MRI is also not suitable for chest surveillance in sarcoma patients as MRI is unable to reliably detect and evaluate small pulmonary metastases (105).

Several technical and workflow considerations require further research and improvement before the widespread implementation of PET/MRI is recommended for sarcoma management.

Future directions with radiotracers

As our understanding of the genetic and molecular foundations of sarcomas and their various histologic subtypes advances, the ongoing development of radiotracers holds the potential to revolutionize the diagnosis, surveillance, and therapeutic strategies for these tumors.

Fibroblast activation protein (FAP) has recently garnered

attention due to its high expression on cancer-associated fibroblasts and absence on normal adult tissues (106). In particular, gallium-68 (^{68}Ga)-labeled FAP inhibitor has demonstrated high uptake in sarcomas with the highest seen SUVmax, often greater than 12 (107-109). When compared to the traditional ^{18}F-FDG radioisotope, ^{68}Ga-FAPI detected more lesions, along with recurrent lesions, with statistically significant higher sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) (110).

The molecular structure of FAP inhibitor molecules allow for the coupling with therapeutic radioisotopes, such as yttrium-90 (^{90}Y), allowing it to be a good theragnostic agent. A recent study demonstrated that ^{90}Y-FAP inhibitor-46 was a safe therapy in patients with sarcoma, resulting in a partial response in 8% of patients tested and stabilization of disease in 50% of patients, demonstrating an outcome that warrants further investigation (111).

Strengths/limitations

This review article is strengthened by its comprehensive coverage of PET/CT clinical applications in orthopedic oncology, spanning references from 1999 to 2024. Furthermore, the inclusion of pertinent patient images enhances understanding of this topic through clinical correlation.

Conclusions

PET imaging is a useful diagnostic, staging, and surveillance tool when evaluating tumors involving the musculoskeletal system, especially sarcomas. When combined with clinical data and other imaging modalities, PET imaging helps in predicting grade of tumors, stage of disease, and in some cases, prognostication. It is important to be aware of musculoskeletal lesions where PET imaging can be most predictive and which lesions may have a higher risk of producing false positive findings. There are potential pitfalls with the use of PET imaging as there are several benign bone and soft tissue lesions with moderate to high PET SUVmax values. A working knowledge of these diseases and the relative sensitivities, specificities, and accuracy percentages for different malignancies of the musculoskeletal system are paramount. Managing these complex cancers requires a multidisciplinary approach involving medical and surgical oncologists, musculoskeletal-specialized radiologists, radiation oncologists, and pathologists. Future research is needed to elucidate new radiographic isotopes and the use of other advanced imaging such as PET-MRI.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The images were obtained from patient cases of the senior author with verbal consent.

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